CASE REPORT

Congenital hypofibrinogenaemia: a presymptomatic detection of an extremely rare bleeding disorder in preterm twins

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SUMMARY

Twenty-eight-week-old preterm monochorionic–diamniotic twins were admitted to the neonatal intensive care unit secondary to low birth weight and mild respiratory distress syndrome. A low fibrinogen level of less than 0.5 g/L was detected following an abnormal full blood count. They required fibrinogen transfusions until 32 weeks corrected gestation to maintain adequate fibrinogen levels. Parental screening revealed that their mother had a previously undiagnosed hypofibrinogenaemia. Of note, her only symptom was menorrhagia. This may have implications on further pregnancies as it can be associated with spontaneous miscarriage and post-partum haemorrhage. Congenital hypofibrinogenaemia is a rare disorder and there are no reported cases from Ireland. A higher degree of suspicion for screening is required to detect new cases and demonstrates the benefits of checking parental levels in such situations.

BACKGROUND

Congenital hypofibrinogenaemia is a rare disorder. Fibrinogen is a glycoprotein synthesised in the liver and plays a critical role in clot formation. The manifestations of a deficiency of fibrinogen can range from minor to life-threatening bleeding or paradoxically thromboembolic events. Early recognition of this disorder could prevent life-threatening and life-limiting complications such as intracranial bleeding. This is particularly relevant in high-risk patients such as preterm and sick neonates as this case illustrates. Hypofibrinogenaemia can have major implications during pregnancy, which also has relevance to this case.

CASE PRESENTATION

Twenty-eight-week-old preterm monochorionic–diamniotic twins were admitted to neonatal intensive care unit secondary to their prematurity, low birth weight and respiratory distress syndrome. They both required surfactant and continuous positive airway pressure initially. They were successfully weaned from respiratory support on day 5 of life. On day 13 of life, twin 1 had recurrent apnoea. A septic work-up along with cultures was performed to investigate for sepsis. Intravenous antibiotics were commenced according to local hospital guidelines. The full blood count of twin 1 revealed thrombocytopenia of $68 \times 10^9/L$. This raised the suspicion of disseminated

intravascular coagulation which prompted a coagulation profile. Twin 1 had a normal prothrombin time and activated partial thromboplastin time with a low fibrinogen level of 0.45 g/L. He was transfused with intravenous plasma-derived fibrinogen concentrate to minimise the risk of intracranial haemorrhage. There was a spontaneous improvement of the platelet count to more than $150 \times 10^9/L$, which suggests that this may have been due to low birth weight and prematurity. The parents are non-consanguineous and there was no known family history of bleeding or coagulation disorders. We investigated for secondary causes of low fibrinogen including liver function tests, a septic work-up and metabolic screening which were normal. A coagulation profile of asymptomatic twin 2 also showed hypofibrinogenaemia with fibrinogen levels being 0.35 g/L initially. After consultation with paediatric haematology, they were both transfused with plasma-derived fibrinogen concentrate to maintain their levels at least greater than 0.75 g/L but preferably 1 g/L. This level was considered safe to minimise life-threatening bleeds, in particular intraventricular haemorrhage (IVH) which, as premature infants they were at risk for. Both parents were screened for the condition and a maternal diagnosis of hypofibrinogenaemia was made. She reported her only symptom being menorrhagia which never required medical treatment and a family history of menorrhagia in her sisters and mother.

The twins were monitored for clinical signs of bleeding, and serial coagulation profiles revealed persistently low levels of fibrinogen. They were managed for prematurity and its complications. Throughout the course of their admission, neither twin manifested clinical signs of prolonged bleeding. Twin 2 developed necrotising enterocolitis on day 23 and required a surgical drain insertion, which was performed under plasma-derived fibrinogen concentrate cover without any bleeding complications. Their serial cranial ultrasounds were normal during their admission. Both were discharged in stable condition to be followed in outpatient clinic. Initial testing on the mother revealed hypofibrinogenaemia and a normal fibrinogen antigen level, 2.44 g/L (1.50–3.07 g/L) signifying both a quantitative and qualitative problem suggestive of a possible hypodysfibrinogenaemia, which may be inherited in an autosomal dominant pattern. They have been referred to paediatric haematology for ongoing follow-up of hypofibrinogenaemia and further

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genetic and molecular investigations. This will be performed several months after cessation of regular intravenous plasma derived fibrinogen concentrate.

EARLY INVESTIGATIONS

- ▶ Full blood count
 - ▶ Peripheral blood film
 - ▶ C-reactive protein
- ▶ Blood culture
 - ▶ Urea and electrolytes
 - ▶ Liver function test
- ▶ Coagulation profile including fibrinogen
 - ▶ Metabolic screening: serum amino acids, acylcarnitine profile and urinary organic acids; maternal coagulation profile and fibrinogen antigen

DIFFERENTIAL DIAGNOSES

- ▶ Sepsis
- ▶ Haemorrhagic disease of the newborn
- ▶ Total parental nutrition-associated liver derangement

TREATMENT

Both twins received intravenous plasma-derived fibrinogen concentrate transfusions in first 4 weeks until they were at 32 weeks corrected gestational age. This is the fibrinogen product issued by the Irish Blood Transfusion Service, replacing cryoprecipitate, due to its decreased risk of pathogen transmission and convenience in usage. Coagulation profiles were performed twice weekly and plasma-derived fibrinogen was transfused if fibrinogen was below agreed thresholds. This was to minimise life-threatening or limiting bleeds such as an intracranial haemorrhage during this vulnerable time. The absence of IVH and bleeding complications may be because of early recognition and monitoring of levels throughout the susceptible neonatal period.

OUTCOME AND FOLLOW-UP

Both were discharged healthy and in a stable condition. Follow-up appointments were arranged with paediatric haematology for further investigation after cessation of regular plasma-derived fibrinogen concentrate and in neonatology outpatient clinic for developmental review. Developmental progress to date has been entirely normal.

DISCUSSION

Congenital hypofibrinogenemia is characterised by an abnormally low level of fibrinogen. It was first described in 1920 in Germany in a young male with repetitive episodes of bleeding.¹ Congenital hypofibrinogenemia is part of an umbrella group of fibrinogen deficiency which also includes afibrinogenemia (<0.2 g/L), dysfibrinogenemia defined as dysfunctional fibrinogen and hypodysfibrinogenemia where there are lower amounts of an abnormal fibrinogen molecule present in the circulation.² It is most commonly due to a heterozygous mutation in one of three genes: *FGA*, *FGB* and *FGG* on chromosome 4. Quantity fibrinogen deficiency may result from deletions, frameshift, non-sense or splicing mutations, all of which can affect fibrinogen synthesis or processing.³

Hypofibrinogenemia can be inherited in an autosomal dominant or recessive fashion. Hypofibrinogenemia is usually autosomal dominantly inherited while afibrinogenemia is more often autosomal recessively inherited. It is equally common in both males and females.⁴ A higher incidence of fibrinogen deficiencies are reported in consanguineous parents.⁵ Registries in

Italy, UK and North America have provided better understanding of these disorders while Iran and India report the most cases.⁵

Fibrinogen is a 340 kDa glycoprotein synthesised in the liver, with a critical role in clot formation. Clinical manifestations of this disorder categorised to specific fibrinogen deficiency are poorly correlated.⁵ One paper showed that 85% of neonates with afibrinogenemia present with bleeding from the umbilical cord.⁵ However, hypofibrinogenemia has been reported with variable presentations ranging from skin bruising to gastrointestinal, genitourinary or intracranial bleeds.⁵ In preterm infants, there is an independent risk factor for intracranial bleeds and therefore their tendency to bleed is further increased.

Diagnosis is made on a coagulation profile. The normal fibrinogen levels are 1.5 to 3.5 g/L. In hypofibrinogenemia, results of coagulation test vary with the amount of fibrinogen present.⁴ In majority of reported cases, plasma fibrinogen level ranges between 0.2 to 1.0 g/L.⁴ A comparison of activity and antigen levels of fibrinogen will help distinguish qualitative defects from quantitative deficiencies. When the functional activity level is low but the antigen level is normal, dysfibrinogenemia or hypodysfibrinogenemia should be considered.

Treatment for active bleeding includes fresh frozen plasma, cryoprecipitate and fibrinogen transfusion.⁶ In July 2009, Irish Blood Transfusion Service replaced cryoprecipitate with plasma-derived fibrinogen concentrate for fibrinogen transfusions to decrease the risk of pathogen transmission. It comes in decreased volumes with faster reconstitution times and does not require thawing or ABO blood group matching.⁷ It is widely recognised in the literature as a standard replacement therapy in hypofibrinogenemia and plasma-derived fibrinogen concentrate is also used in the USA and the UK.⁸ However, plasma-derived fibrinogen can still predispose patients to the attached risks of blood products such as transfusion reaction, infection and transfusion-related acute lung injury.⁵ Fibrinogen transfusion also carries a risk of allergic reaction, inhibitory antibodies formation and thrombotic complication.⁵

Therefore, the decision to transfuse must be balanced with the risk of bleeding. The aim of managing hypofibrinogenemia to prevent a life-threatening bleed, such as an intracranial haemorrhage, which is the leading cause of death.⁵ However, there are limited guidelines regarding the treatment of hypofibrinogenemia, particularly within this particular patient group. Therefore, further awareness and research in the management of this condition is needed.

Patient's perspective

- ▶ "It was very important to me that it was picked up but I did not understand the risk factors the issue would pose to my sons. Brain scans, blood tests and transfusions were all confusing to me but I am now aware of further support that can be offered to my sons."—Mother of the patients

Learning points

- ▶ Although rare, hypofibrinogenemia should be considered as a differential diagnosis for an abnormal coagulation profile.
- ▶ Maintaining adequate levels is important in vulnerable patient groups such as preterm neonates. A diagnosis in one patient should raise the suspicion of the diagnosis in other family members.

Contributors The patient was initially under the care of NM while on call and reviewed on ward rounds by MAB. MAB suggested writing up the case given the rare diagnosis made. MIR and CMB took an active role in the work up and treatment of the patients. CMB and MIR contributed equally to this paper.

Competing interests None declared.

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